Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

tocilizumab, both when used alone and in combination therapy. We hypothesized that the reason for the survival difference between steroids alone vs tocilizumab alone was possibly the delayed onset of action of tocilizumab in addition to its later administration. On the contrary, we surmise that, in the steroids plus tocilizumab combination group, steroids provided an initial immunosuppressive effect that was enhanced and sustained by tocilizumab. The importance of the timing of drug administration on survival is also emphasized in the correspondence by Martinez-Urbistondo et al.[2]

Our study demonstrated increased survival with corticosteroid use in hospitalized patients with laboratory evidence of hyperinflammation, when compared with standard of care. This finding has been supported by published randomized controlled studies, although the studies did not particularly select patients with hyperinflammation. However, randomized controlled studies have failed to show benefit of anti-IL6 therapies in COVID-19. These studies did not include critically ill patients, had small sample sizes, and included worsening oxygenation in the composite primary outcome. In the study of Hermine et al,[3] the authors note very wide CIs and decreased need for mechanical ventilation and death in the tocilizumab arm. In the tocilizumab arm, 33% of the patients received concomitant corticosteroids, although the timing in relation to tocilizumab is not known. The mortality rate in these studies was also far lower than in our cohort, regardless of the treatment arm. Although a large observational study[4] that included critically ill patients reported increased survival with combination therapy, in our opinion, the questions of whether tocilizumab and steroid combination decreases mortality rates in patients with severe COVID-19 infection when compared with steroid therapy alone has not yet been answered.

The proposed postulate of genetic polymorphisms that contribute to corticosteroid resistance is indeed interesting and warrants further investigation. We agree that clinical trials must be designed to evaluate the benefit of combination therapy in patients with COVID-19, with timing being key to the trial design. We want to emphasize the increased risk of infections observed in patients who receive combination immunosuppressive therapies vs steroids or tocilizumab alone.

Although increased infection rate may have been due to factors such as central lines and other critical illness-related procedures, adverse drug effects and complications should be monitored carefully in the future randomized trials to access properly the risk-benefit ratio of immunosuppressive therapy in severe COVID-19 infection.

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Remarks About Retrospective Analysis of Ivermectin Effectiveness on Coronavirus Disease 2019 (ICON Study)

To the Editor:

We read with interest the article in *CHEST* (January 2021) by Rajter et al,[1] a retrospective study examining 280 hospitalized patients with coronavirus disease 2019 (COVID-19), which concluded that ivermectin was associated with lower overall mortality.

We think that the study did not report two important variables that would have influenced the outcome. The first is time of symptom onset. We cannot know what the patients' COVID-19 infection stage was at admission. We already know that corticosteroids are effective for mortality reduction only in the second week after

symptom onset.[2] The second is patients' health insurance coverage. In the American context, it is possible that uninsured patients, or those unable to afford hospitalization fees, would have delayed admission.[3]

An important concern is that the used dose of ivermectin (200 μg/kg) reaches a plasmatic concentration much lower than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 50% inhibitory concentration at pulmonary tissue (<35 times inferior).[4]

We highlight that the study considered all-cause mortality as the main outcome while evaluating only pulmonary severity. We consider that the severe pulmonary compromise category in the study is a heterogeneous one, grouping patients with different clinical statuses. The mortality trend through time was assessed as inconsistent, but a minimal variation in deaths or classification of severity would change statistical significance, so we believe it is relevant to show mortality trends over weeks.

A caliper distance difference for propensity score matching (0.2, instead of, eg, 0.25) would risk introducing an additional selection bias. For example, a patient that received two doses of ivermectin and died was not included. If only one additional death would be included in the ivermectin treatment group, the OR for mortality would have changed from 0.47 (CI, 0.22-0.99) to 0.51 (CI, 0.25-1.05).

Finally, in the study, the sex OR for mortality is nonstatistically significant, when there are studies that find a clear relationship between these two variables.[3,5] Taking into consideration that age and sex are powerful confounders for mortality, we would have wished deaths by age and sex to be presented.

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Standard Dose Ivermectin for COVID-19

To the Editor:

The article by Ceplowicz Rajter et al[1] published in *CHEST* (January 2021), which presents a significant effect of ivermectin at standard dose on COVID-19 mortality rates, raises once again important questions on the significance of observational studies that report posttreatment outcome for COVID-19. Uncontrolled, observational studies have already created confusion in the medical community's response to the pandemics, the example of hydroxychloroquine being the most obvious one.[2] For instance, in their article, the criteria for treatment with ivermectin are not specified, and a bias due to treatment indication is not addressed completely. Moreover, despite the use of a propensity score matching aimed at reducing confounders, relevant variables might have been measured inadequately. As an example, the authors did not find a benefit associated with the use of steroids (which were given in a significantly higher proportion of patients in the ivermectin group of the unmatched cohort) and suppose that this finding, in contrast to what has been demonstrated by the RECOVERY clinical trial,[3] might be due to a propensity to save this treatment for the most critically ill patients.

In addition to the limitations due to the study design, we would like to point out the concerns about the dose of ivermectin that has been used.

Indeed, based on the article by Caly et al,[4] the potential drug efficacy in vitro was observed at high ivermectin concentration. The IC-50 reported (2,190 ng/mL) was at least 50 times higher than the maximal concentration achievable with the standard dose of 200 μg/kg, which is